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PHARMACODYNAMIC ASPECTS OF SYSTEMIC DRUG DELIVERY

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ABSTRACT

Some of the most common cases of drug delivery (i.v. bolus, first-order absorption and zero-order absorption) are evaluated with respect to the relationship between extent and/or rate of drug absorption and pharmacodynamic outcome. Each case is evaluated after a single dose and at steady state after multiple dosing in a one-compartment body model. The pharmacodynamic model used is the E_{max}-model with and without an effect compartment. The area under the effect-time curve (AUC_E) is used as a cumulative measure for overall drug activity. After first-order absorption, AUC_E can vary as a function of absorption rate between a minimum, the AUC_E of the equivalent i.v. bolus, E_{max}/k_e*ln[1+D/(E_{50}*Vd)], and a maximum, E_{max}*D/(E_{50}*CL). After multiple dosing, the degree of fluctuation of the pharmacodynamic effect will depend on the dose and will always be less than the degree of pharmacokinetic fluctuation. A dosing rate ($DR_{50}=CL*E_{50}/f_u$) is proposed that allows calculation of the dose necessary to produce and maintain 50% of the maximum effect and that can easily be adapted to obtain any fraction of the desired effect. Zero-order input rate is optimal to achieve the maximum cumulative effect with a minimal amount of drug. For multiple dosing, a multiple dose factor (MDF) is introduced that allows calculation of the additional dose needed to maintain a certain minimum level of effect at all times. The relationships between drug delivery and pharmacodynamic effect should be

appreciated and preferable over mere blood levels in the development of drug delivery systems and the design of rational dosage regimens.

During the past 30 years significant knowledge has been gained on the issue of bioavailability as measured by systemic concentrations of drugs. For the most common case of drugs which follow linear pharmacokinetics, the area under the curve (AUC) is directly proportional to the amount of drug absorbed. Therefore, AUC is an excellent indicator of the extent of drug absorption. For equal amounts absorbed, AUC is constant and independent of the rate of absorption. Furthermore, AUC allows prediction of the average steady state levels during multiple dosing. The rate of absorption is usually characterized by the time (t_{max}) and magnitude (C_{max}) of the peak level or by means of appropriate absorption rate constants. The rate of absorption determines the degree of fluctuation during multiple dosing.

With the advent of PK-PD modeling in recent years, it has become common to measure not only the resulting plasma levels for different dosage forms, but also to quantify the resulting drug effects as a function of time. Just like in the case of pharmacokinetics, the area under the effect-time curve (AUC_E) can be used as a cumulative measure of drug activity. The goal of this paper is to evaluate some of the most common cases of drug delivery with respect to the relationship between drug delivery and pharmacodynamic outcome.

PROCEDURES

Investigated PK-PD Models

To illustrate the effect of different drug delivery properties on the resulting pharmacodynamics, the three most common rates of drug input were compared: i.v. bolus, first order absorption and zero-order absorption. Each case was evaluated after a single dose and at steady state after multiple dosing in a one-compartment body model. The plasma concentrations (Cp) were calculated using the following equations:

1. i.v. bolus, single dose

$$Cp = \frac{D}{Vd} \cdot e^{-k_e t} \qquad \text{(eq. 1)}$$

2. i.v. bolus, multiple dose at steady state

$$Cp = \frac{D}{Vd} \cdot \frac{e^{-k_e t}}{1 - e^{-k_e \tau}} \qquad \text{(eq. 2)}$$

3. first order absorption, single dose

$$Cp = \frac{D \cdot k_a}{Vd \cdot (k_a - k_e)} \cdot (e^{-k_e t} - e^{-k_a t}) \quad \text{(eq. 3)}$$

4. first order absorption, multiple dose at steady state

$$Cp = \frac{D \cdot k_a}{Vd \cdot (k_a - k_e)} \cdot \left(\frac{e^{-k_e t}}{1 - e^{-k_e \tau}} - \frac{e^{-k_a t}}{1 - e^{-k_a \tau}}\right) \quad \text{(eq. 4)}$$

5. zero order absorption, single dose

$$Cp = \frac{k_o}{k_e \cdot Vd} \cdot (e^{k_e T} - 1) \cdot e^{-k_e t} \quad \text{(eq. 5)}$$

6. continuous zero order absorption, steady state

$$Cp = \frac{k_o}{k_e \cdot Vd} \quad \text{(eq. 6)}$$

where D=bioavailable dose, Vd=volume of distribution, k_e=elimination rate constant, k_a=first order absorption rate constant, k_o=zero order absorption rate constant, T=duration of zero order absorption (T=t during absorption and constant in the post-absorption phase), τ=dosing interval and t=time after the last dose was administered.

The pharmacodynamic model used was the E_{max}-model which relates concentration, C, and effect, E, using the following expression:

$$E = \frac{E_{max} \cdot C}{E_{50} + C} \quad \text{(eq. 7)}$$

where E_{max} is the maximum effect possible (100%), and E_{50} is the concentration at which 50% of the maximum effect is observed.

For all simulations in this presentation E_{50} was assumed to be 10 ng/mL, Vd was assumed to be 100 L and k_e was kept constant at 0.2 h^{-1}. This is equivalent to a total body clearance of 20 L/h. Dose, k_a and k_o were varied in order to evaluate their contribution.

For the concentration, C, in eq. 7, two approaches were tested.

The first approach assumes the biophase is identical with the pharmacokinetic compartment and uses either the total concentration, Cp, or the respective free, unbound concentration, f_u*Cp, where f_u is the fraction unbound to plasma proteins. This is relevant since only the unbound drug concentration will be responsible for drug activity.

The second approach assumes a hypothetical effect compartment exists (Fig. 1). It uses Ce, the concentration in the compartment hypothesized to cause the drug effect. Corresponding parameters are rate constants for distributing drug to (k_{ie}) and from (k_{eo}) this compartment (1, 2). This approach has been shown to be very useful for modeling situations with delays in the onset and disappearance of

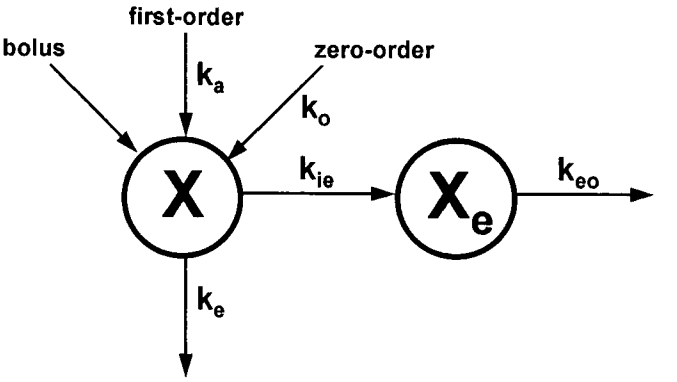

FIGURE 1

Pharmacokinetic-pharmacodynamic model. k_a = first-order absorption rate constant, k_o = zero-order absorption rate constant, X = amount of drug in the pharmacokinetic compartment, X_e = amount of drug in the hypothetical effect compartment, k_{ie} = transfer rate constant into the effect compartment, k_{eo} = transfer rate constant out of the effect compartment.

drug action. Based on the model shown in Fig. 1, equations can be derived for the concentration-time profile within the effect compartment. The rate of change of the amount of drug in the effect compartment (X_e) is

$$\frac{dX_e}{dt} = k_{ie} \cdot X - k_{eo} \cdot X_e \qquad \text{(eq. 8)}$$

where X is the amount of drug in the kinetic compartment. For the simplest case of a single i.v. bolus, integration results in

$$X_e = \frac{D \cdot k_{ie}}{(k_{eo} - k_e)} \cdot (e^{-k_e t} - e^{-k_{eo} t}) \qquad \text{(eq. 9)}$$

At steady state the concentration in the effect compartment (Ce) will be equal to Cp, and the rate of input, k_{ie}*X, will equal that of the output, k_{eo}*X_e. This assumption allows calculation of the volume of distribution for the effect compartment (V_e):

$$V_e = \frac{k_{ie}}{k_{eo}} \cdot Vd \qquad \text{(eq. 10)}$$

Hence, it is possible to calculate equations for the hypothetical concentrations in the effect compartment by dividing X_e by V_e. It is noteworthy that the input rate constant, k_{ie}, cancels out in this procedure (eq. 11-16) and is of no significance for the concentration profile in the effect compartment.

In a similar way the concentration-time profiles in the effect compartment can be calculated for the other cases and result in the following equations:

1. i.v. bolus, single dose

$$Ce = \frac{D \cdot k_{eo}}{Vd \cdot (k_{eo} - k_e)} \cdot (e^{-k_e t} - e^{-k_{eo} t}) \qquad \text{(eq. 11)}$$

2. i.v. bolus, multiple dose at steady state

$$Ce = \frac{D \cdot k_{eo}}{Vd \cdot (k_{eo} - k_e)} \cdot \left(\frac{e^{-k_e t}}{1 - e^{-k_e \tau}} - \frac{e^{-k_{eo} t}}{1 - e^{-k_{eo} \tau}}\right) \qquad \text{(eq. 12)}$$

3. first order absorption, single dose

$$Ce = \frac{D \cdot k_a \cdot k_{eo}}{Vd} \cdot \left(\frac{e^{-k_e t}}{(k_a - k_e) \cdot (k_{eo} - k_e)} + \frac{e^{-k_a t}}{(k_e - k_a) \cdot (k_{eo} - k_a)} + \frac{e^{-k_{eo} t}}{(k_e - k_{eo}) \cdot (k_a - k_{eo})}\right) \qquad \text{(eq. 13)}$$

4. first order absorption, multiple dose at steady state

$$Ce = \frac{D \cdot k_a \cdot k_{eo}}{Vd} \cdot \left(\frac{e^{-k_e t}}{(k_a - k_e) \cdot (k_{eo} - k_e) \cdot (1 - e^{-k_e \tau})} + \frac{e^{-k_a t}}{(k_e - k_a) \cdot (k_{eo} - k_a) \cdot (1 - e^{-k_a \tau})} + \frac{e^{-k_{eo} t}}{(k_a - k_{eo}) \cdot (k_e - k_{eo}) \cdot (1 - e^{-k_{eo} \tau})}\right) \qquad \text{(eq. 14)}$$

5. zero order absorption, single dose

$$Ce = \frac{k_o}{k_e \cdot Vd \cdot (k_{eo} - k_e)} \cdot \left(k_{eo} \cdot (e^{k_e T} - 1) \cdot e^{-k_e t} - k_e \cdot (e^{k_{eo} T} - 1) \cdot e^{-k_{eo} t}\right) \qquad \text{(eq. 15)}$$

6. continuous zero order absorption, steady state

$$Ce = \frac{k_o}{k_e \cdot Vd} \qquad \text{(eq. 16)}$$

C is the free, unbound concentration, f_u*Ce, where f_u is the fraction unbound to plasma proteins, when protein binding is considered.

Area Under The Effect-Time Curve (AUC_E)

The area under the effect-time curve (AUC_E) can be used as a cumulative measure for overall drug activity. AUC_E can be obtained by integration of the respective effect-time relationships. However, an explicit solution is only available in the case of an i.v. bolus injection without an effect compartment. In this case, the effect-time relationship is given by

$$E = \frac{E_{max} \cdot D \cdot e^{-k_e t}}{E_{50} \cdot Vd + D \cdot e^{-k_e t}} \qquad \text{(eq. 17)}$$

Integration yields

$$AUC_E = \int_0^\infty E \cdot dt = \frac{E_{max}}{k_e} \cdot \ln\left(1 + \frac{D}{E_{50} \cdot Vd}\right) \qquad \text{(eq. 18)}$$

For the other cases, only numerical integration is possible. For the simulations shown in this paper, numerical integration was performed using MathCad (3).

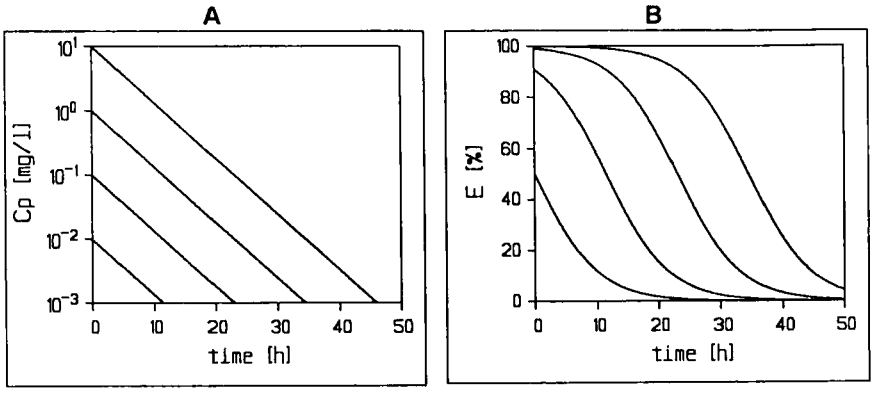

FIGURE 2

Pharmacokinetic (A) and pharmacodynamic (B) profiles for a drug administered in four different doses (1, 10, 100 and 1000 mg) by intravenous bolus injection. Assumed pharmacokinetic parameters are k_e=0.2 h^{-1} and Vd =100 l, assumed pharmacodynamic parameters are E_{max} = 100 % and E_{50} = 0.01 mg/l.

RESULTS

Single I.V.-Bolus Without Effect Compartment

Fig. 2 shows the effect-time curves for four different doses. As expected, the increase in effect is not proportional to the dose. As can be seen from eq. 18 for higher doses ($D>>E_{50}*Vd$), the increase in cumulative effects as expressed by AUC_E is proportional to the natural logarithm of the dose (Fig. 3). This relationship has been experimentally observed in studies on the pharmacodynamics of methylprednisolone (4,5).

One characteristic number is the D_{50} which is the amount in the body that produces 50% of the maximum effect. D_{50} can be expressed as

$$D_{50} = E_{50} \cdot Vd \qquad \text{(eq. 19)}$$

Hence, it follows that if $D=D_{50}$ the initial concentration will be E_{50} and the initial effect $0.5*E_{max}$. The total area under the effect-time curve for this dose will be $E_{max}*\ln(2)/k_e$ or $E_{max}*t_{1/2}$.

If protein binding is considered, then D_{50} should be expressed as the amount in

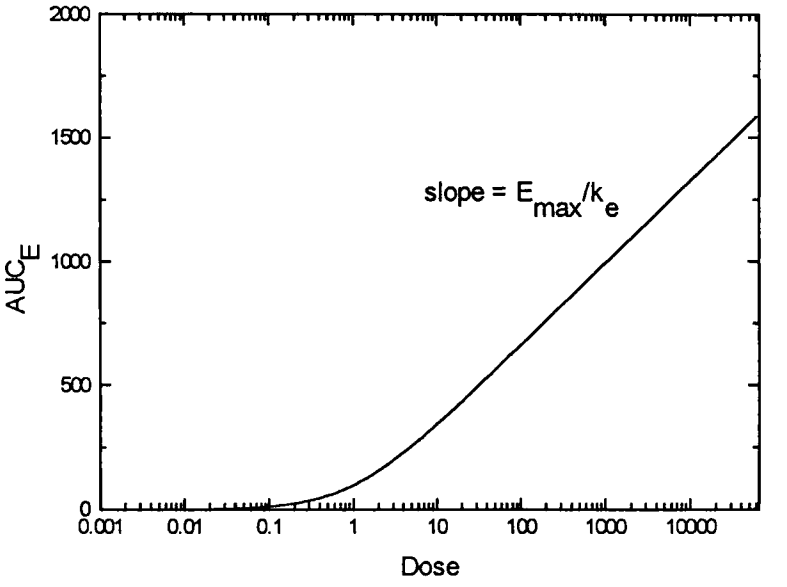

FIGURE 3

Relationship between dose and area under the effect-time curve (AUC_E) after intravenous bolus injection. Assumed pharmacokinetic parameters are k_e=0.2 h^{-1} and Vd =100 l, assumed pharmacodynamic parameters are E_{max} = 100 % and E_{50} = 0.01 mg/l.

the body that produces a free concentration of E_{50} in the body:

$$D_{50} = \frac{E_{50} \cdot Vd}{f_u} \qquad \text{(eq. 20)}$$

where f_U is the fraction unbound to plasma proteins.

It is obvious from Fig. 3 that dose and effect are not changing proportional. For doses that exceed D_{50}, the fractional increase, f, of the cumulative effect measured by AUC_E after an n-fold change in dose can quickly be calculated as

$$f = \frac{\ln n}{\ln D - \ln D_{50}} \qquad \text{(eq. 21)}$$

An example may illustrate the usefulness of eq. 21. For methylprednisolone, D_{50} can be estimated to be 0.5 mg. Hence, doubling of the dose from 10 to 20 mg (n=2) will result in an increase of 23% in cumulative effect; doubling of the dose from 100 to 200 mg will increase the effect by 13% and doubling from 1000 mg to 2000 mg will increase the effect by 9%.

Continuous Zero Order Absorption to Steady State

Since all concentrations in the body are in equilibrium at steady state, the model will be identical with and without an effect compartment. The dosing rate that will produce 50% of the maximum effect is called DR_{50} and is defined as

$$DR_{50} = E_{50} \cdot CL \qquad \text{(eq. 22)}$$

where CL is the total body clearance of the drug. If protein binding is included in the consideration, than DR_{50} is the dosing rate that will produce and maintain a free concentration of E_{50} in the body and is defined as:

$$DR_{50} = \frac{E_{50} \cdot CL}{f_u} \qquad \text{(eq. 23)}$$

The dosing rate DR_{50} can easily be converted to a dosing rate for any other fraction (x%) of E_{max} as:

$$DR_x = \frac{x}{(100 - x)} \cdot DR_{50} \qquad \text{(eq. 24)}$$

For example, the dosing rate to produce and maintain 80% of E_{max} is $DR_{80}=4*DR_{50}$. The dosing rate to produce and maintain 90% of E_{max} is $DR_{90}=9*DR_{50}$.

Multiple I.V. Bolus Without Effect Compartment

The average steady state concentrations are defined in identical terms as the steady state concentrations after continuous zero order absorption. Hence, eq. 22-24 apply except with a pulsing input rate D/τ instead of a continuous dosing rate. However, during multiple dosing, the plasma concentrations fluctuate between a peak concentration, Cp_{max}, and a trough concentration, Cp_{min}. They can be calculated as

$$Cp_{max} = \frac{D}{Vd \cdot (1 - e^{-k_e \tau})} \qquad \text{(eq. 25)}$$

and

$$Cp_{min} = \frac{D \cdot e^{-k_e \tau}}{Vd \cdot (1 - e^{-k_e \tau})} \qquad \text{(eq. 26)}$$

Hence, the fluctuation, F, between peak and trough is expressed as the ratio of the two values. It depends only on half-life and dosing interval and is independent of the dose:

$$F = \frac{C_{max}}{C_{min}} = \frac{1}{e^{-k_e \tau}} = e^{k_e \tau} \qquad \text{(eq. 27)}$$

The respective effects E_{peak} and E_{trough} can be calculated as:

$$E_{peak} = \frac{E_{max} \cdot C_{max}}{E_{50} + C_{max}} = \frac{E_{max} \cdot D}{D_{50} \cdot (1 - e^{-k_e \tau}) + D} \qquad \text{(eq. 28)}$$

and

$$E_{trough} = \frac{E_{max} \cdot C_{min}}{E_{50} + C_{min}} = \frac{E_{max} \cdot D \cdot e^{-k_e \tau}}{D_{50} \cdot (1 - e^{-k_e \tau}) + D \cdot e^{-k_e \tau}} \quad \text{(eq. 29)}$$

The fluctuation in effect (F_E) can be expressed as the ratio of these two numbers:

$$F_E = \frac{E_{peak}}{E_{trough}} = \frac{C_{max} \cdot (E_{50} + C_{min})}{C_{min} \cdot (E_{50} + C_{max})} \quad \text{(eq. 30)}$$

Eq. 30 shows that since $C_{max} > C_{min}$, the degree of fluctuation for the pharmacokinetics will always exceed the degree of fluctuation for the pharmacodynamics. For very low concentrations (C_{max} and $C_{min} << E_{50}$) the pharmacodynamic fluctuation will approach the pharmacokinetic fluctuation. For high concentrations (C_{max} and $C_{min} >> E_{50}$) the pharmacodynamic fluctuation of the effect will approach zero.

If a dosing regimen is to be designed ensuring that a certain target concentration (Cp_{target}) is maintained at all times, the dosing regimen using a minimum amount of drug will be the continuous zero order input, $k_0 = Cp_{target} * CL$. If multiple dosing is to be chosen, than more drug is needed to obtain the same pharmacodynamic outcome. The minimum dose per dosing interval needed to stay above the target concentration at all times can be calculated as

$$D = \frac{Cp_x \cdot Vd \cdot (1 - e^{-k_e \tau})}{e^{-k_e \tau}} = \frac{k_0 \cdot (1 - e^{-k_e \tau})}{k_e \cdot e^{-k_e \tau}} = k_0 \cdot MDF \quad \text{(eq. 31)}$$

where MDF is a multiple dose factor that quantifies how much more drug is needed with multiple dosing in comparison to continuous zero order administration. MDF is a function of dosing interval and half-life and can be rearranged to give

$$MDF = 1.44 \cdot t_{1/2} \cdot (2^{(\frac{\tau}{t_{1/2}})} - 1) \quad \text{(eq. 32)}$$

Some examples can illustrate eq. 32. If the dosing interval is equal to one half-life, then 144% of the equivalent zero-order dose is needed. If the dosing interval is 50% of the half-life, 119% of drug is needed; When selected dosing intervals are 2, 3 and 4 half-lives, then 216%, 336% and 540% of the zero-order dose is needed, respectively.

First Order Absorption Without an Effect Compartment

Fig. 4 shows the pharmacokinetic and pharmacodynamic profiles for four different doses with four different rates of absorption. It is clear from the curves that the effect-time curves (right side) behave very differently than the

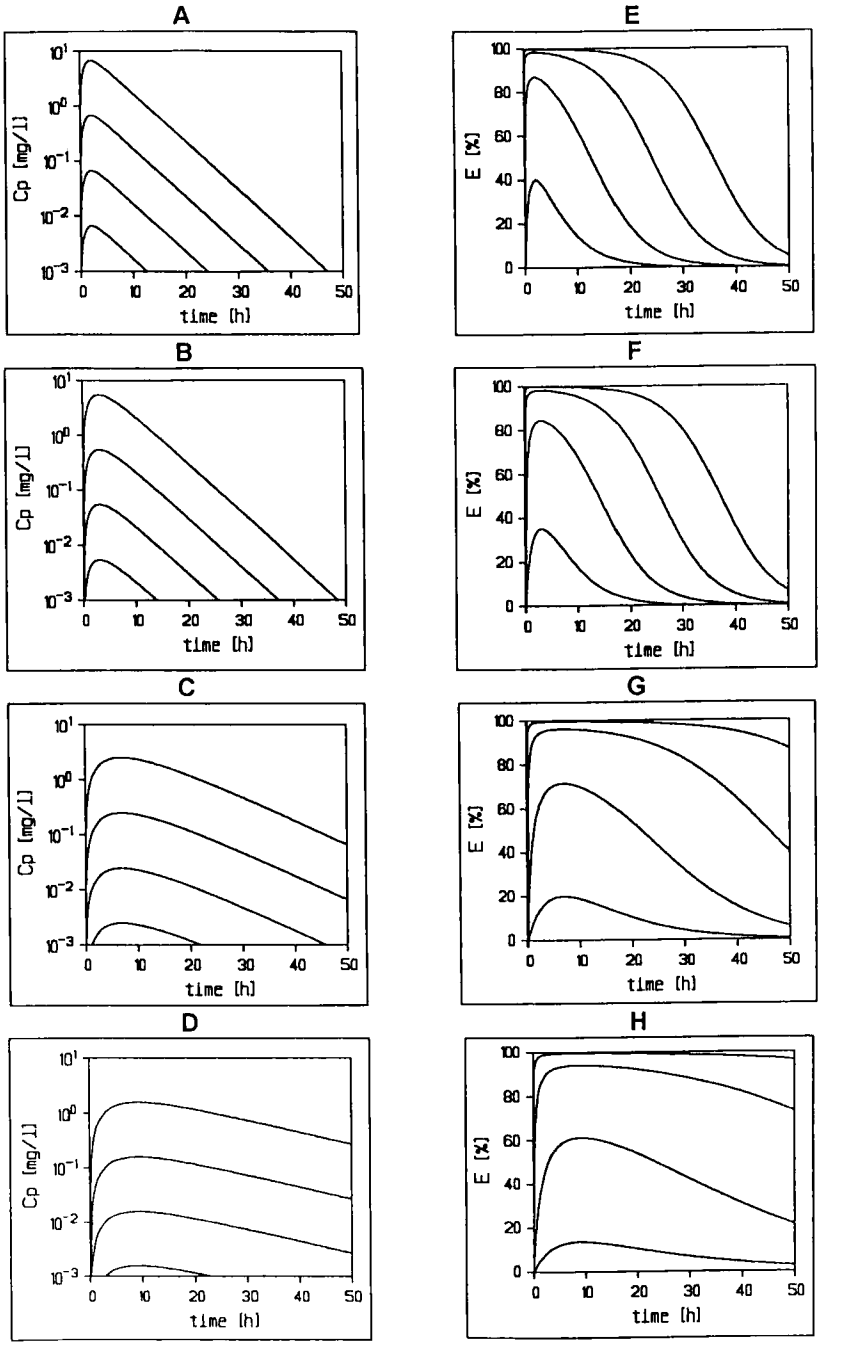

FIGURE 4

Pharmacokinetic (A-D) and pharmacodynamic (E-H) profiles for a drug administered in four different doses (1, 10, 100 and 1000 mg) by first-order absorption. Absorption rate constants (k_a) varied from 1 (A, E), 0.5 (B, F), 0.1 (C, G) and 0.05 h^{-1} (D, H). Assumed pharmacokinetic parameters are k_e = 0.2 h^{-1} and Vd = 100 l, assumed pharmacodynamic parameters are E_{max} = 100 % and E_{50} = 0.01 mg/l.

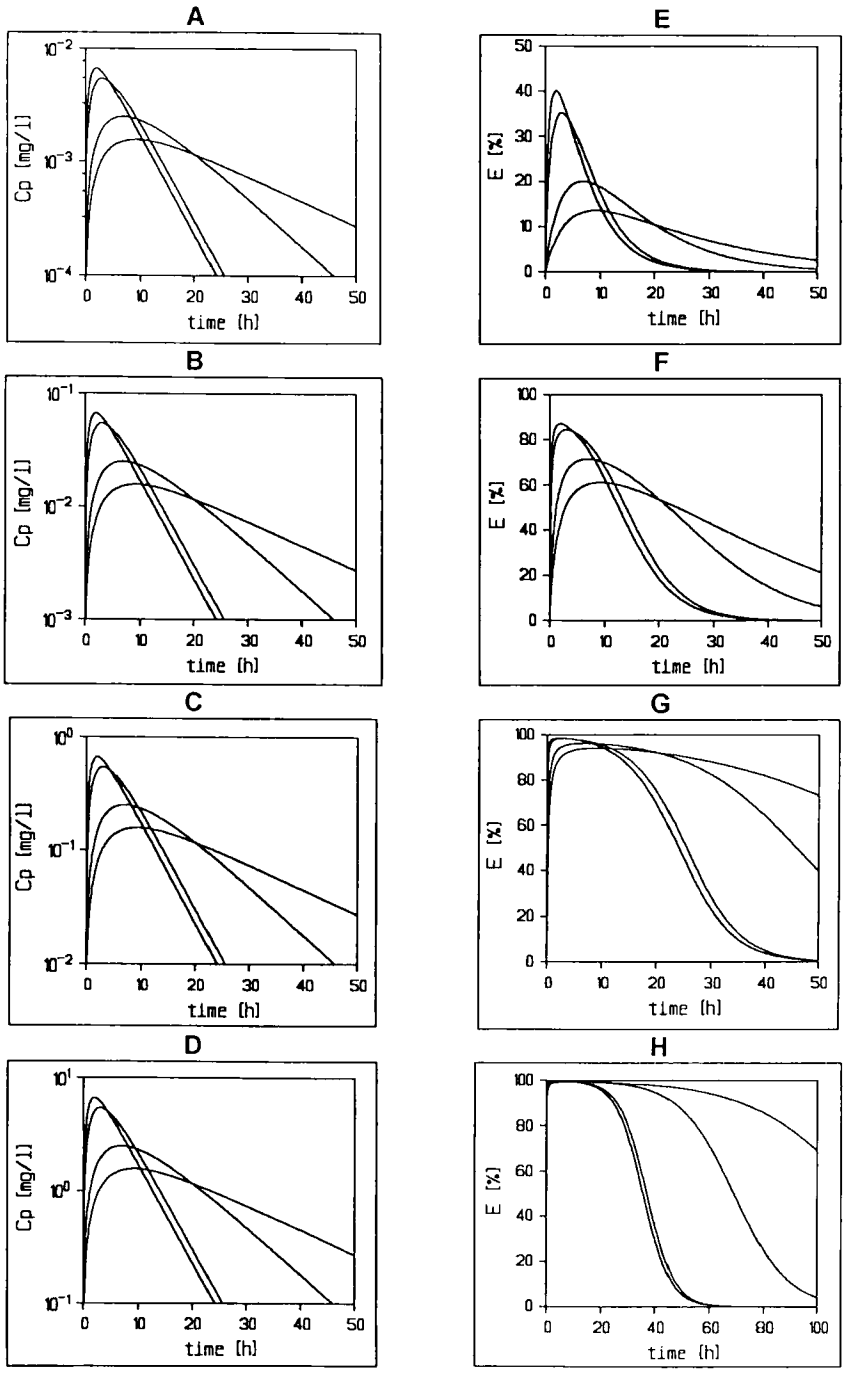

FIGURE 5

Pharmacokinetic (A-D) and pharmacodynamic (E-H) profiles for a drug administered in four different absorption rates (0.05, 0.1, 0.5 and 1 h^{-1}) by first-order absorption. Dose varied from 1 (A, E), 10 (B, F), 100 (C, G) and 1000 mg (D, H). Assumed pharmacokinetic parameters are k_e = 0.2 h^{-1} and Vd = 100 l, assumed pharmacodynamic parameters are E_{max} = 100 % and E_{50} = 0.01 mg/l.

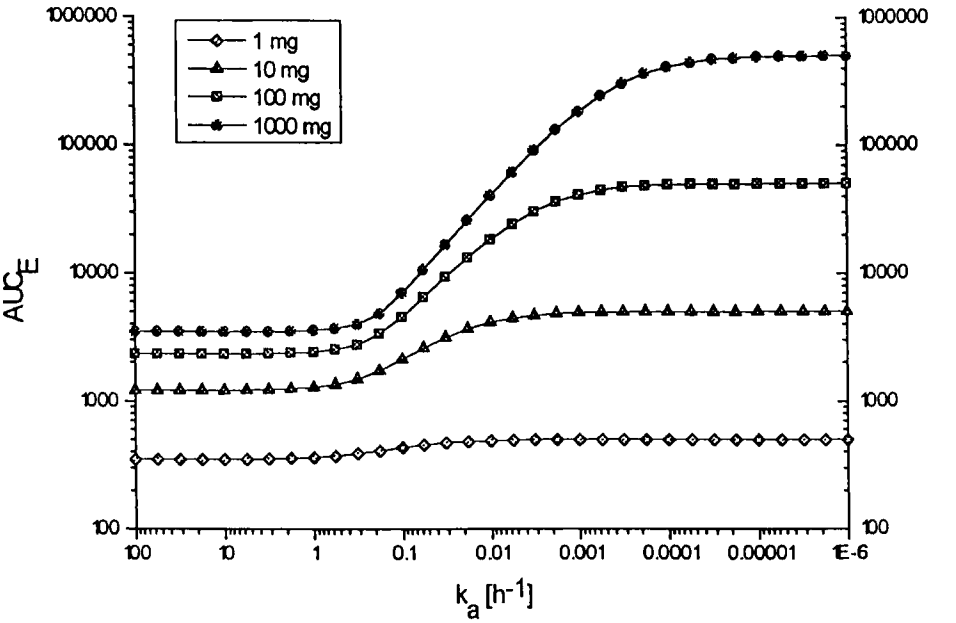

FIGURE 6

Relationship between first-order absorption rate constant k_a and area under the effect-time curve (AUC_E) for four different doses (1, 10 , 100 and 1000 mg.). Assumed pharmacokinetic parameters are k_e = 0.2 h^{-1} and Vd = 100 l, assumed pharmacodynamic parameters are E_{max} = 100 % and E_{50} = 0.01 mg/l.

concentration-time curves (left side). Fig. 5 shows the effect of different absorption rates for the same dose in four cases. Whereas the pharmacokinetic profiles are superimposable, the pharmacodynamic curves vary dramatically.

Unfortunately, it is not possible to derive an expression for the area under the effect-time curve (AUC_E) after first-order absorption. However, using numerical integration, it is possible to calculate the individual AUC_E and plot is as a function of absorption rate (Fig. 6). The figure shows that for absorption rate constants that exceed the elimination rate constant (k_e=0.2 h^{-1}), there is little change in the AUC_E. For rapid absorption, the AUC_E approaches the expression shown in eq. 18 for i.v. bolus injection which is $AUC_{E(min)}$, the smallest AUC_E possible:

$$AUC_{E_{min}} = \frac{E_{max}}{k_e} \cdot \ln(1 + \frac{D}{D_{50}}) \qquad \text{(eq. 33)}$$

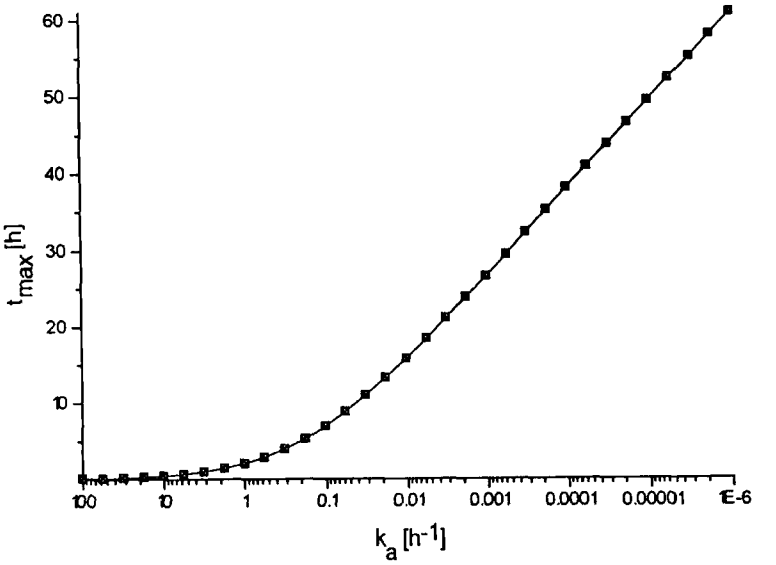

FIGURE 7

Relationship between first-order absorption rate constant k_a and time of the maximum effect and concentration (t_{max}). This time point is independent of dose. Assumed pharmacokinetic parameters are k_e = 0.2 h^{-1} and Vd = 100 l, assumed pharmacodynamic parameters are E_{max} = 100 % and E_{50} = 0.01 mg/l.

When the absorption slows down, AUC_E increases in dose-dependent way. Whereas the increase is small for low doses ($D<D_{50}$), it can be significant for higher doses. The maximum AUC_E will be achieved with extremely slow absorption rates (k_a approaches 0) that result in extremely low concentrations ($Cp<<E_{50}$). Hence, the effect is directly proportional to concentration in this case:

$$E = \frac{E_{max}}{E_{50}} \cdot C \qquad \text{(eq. 34)}$$

and the maximal $AUC_{E(max)}$ can be obtained by integration as

$$AUC_{E_{max}} = \frac{E_{max} \cdot D}{E_{50} \cdot k_e \cdot Vd} = \frac{E_{max} \cdot D}{k_e \cdot D_{50}} \qquad \text{(eq. 35)}$$

It should be pointed out that the approach of maximizing AUC_E by decreasing absorption rate is not very practical since the resulting low concentrations most like will not be sufficient for therapeutic effects.

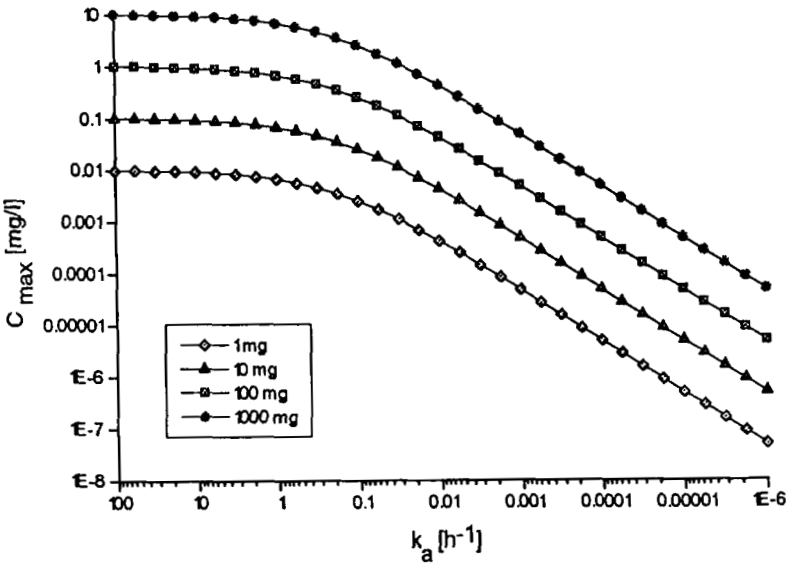

FIGURE 8

Relationship between first-order absorption rate constant k_a and maximum plasma concentration (C_{max}) for four different doses (1, 10 , 100 and 1000 mg.). Assumed pharmacokinetic parameters are k_e = 0.2 h^{-1} and Vd = 100 l, assumed pharmacodynamic parameters are E_{max} = 100 % and E_{50} = 0.01 mg/l.

Combination of eq. 33 and 35 allows calculation of the maximum increase of cumulative effect by modification of absorption rate, expressed as the ratio of $AUC_{E(max)}$ and $AUC_{E(min)}$:

$$\frac{AUC_{E_{max}}}{AUC_{E_{min}}} = \frac{D}{D_{50} \cdot \ln(1+\frac{D}{D_{50}})} \qquad \text{(eq. 36)}$$

For the case that $D=D_{50}$, this ratio would be 1.44 indicating a 44 % increase in cumulative effect. If D exceeds D_{50} by 1000-fold (Fig. 6), the increase is 145-fold.

Fig. 7 shows the effect of changing absorption rates on the time of the maximum effect which also is the time of the maximum concentration:

$$t_{max} = \frac{\ln\left(\frac{k_a}{k_e}\right)}{k_a - k_e} \qquad \text{(eq. 37)}$$

The maximum concentration, C_{max}, at time, t_{max}, (Fig. 8) can be calculated from

$$C_{max} = \frac{D}{Vd} \cdot e^{-k_e t_{max}} \qquad \text{(eq. 38)}$$

Hence, C_{max} is directly proportional to dose. Fig. 8 also shows that C_{max} changes as a function of absorption rate constant much more quickly if $k_e > k_a$ (flip-flop case).

Fig. 9 shows the respective maximum effects, E_{peak} as a function of k_a. E_{peak} was calculated by substitution of C_{max} for C in eq. 7.

$$E_{peak} = \frac{E_{max} \cdot C_{max}}{E_{50} + C_{max}} \qquad \text{(eq. 39)}$$

As expected, for higher doses and rapid absorption E_{peak} will approach E_{max} whereas for lower doses and slower absorption, E_{peak} will be considerably lower.

Single I.V. Bolus With Effect Compartment

Just as eq. 3 and eq. 12 are identical with k_{eo} substituted for k_a, eq. 33 to 39 can be adjusted for the case of an effect compartment after i.v. bolus injection by substituting k_a with k_{eo}. Also in Fig. 4-9, k_a can be substituted by k_{eo} and then be used to evaluate the situation with an effect compartment after i.v. bolus dosing.

Zero Order Absorption Without Effect Compartment

Fig. 10 shows the pharmacokinetic and pharmacodynamic profiles for four different doses administered with zero-order absorption. While the pharmacokinetic profile shows dose-proportionality, the pharmacodynamic curves are not proportional in magnitude or shape.

Fig. 11 shows the result after zero-order administration of the same dose at four different input rates and four different dose levels. Just as in the case of first-order absorption, superimposable curves are observed for the pharmacokinetic profiles, however, there are dramatic differences in the pharmacodynamic profiles.

DISCUSSION

The described examples show the complexity of the relationship between drug delivery rate and pharmacodynamic effects as a function of time. Most

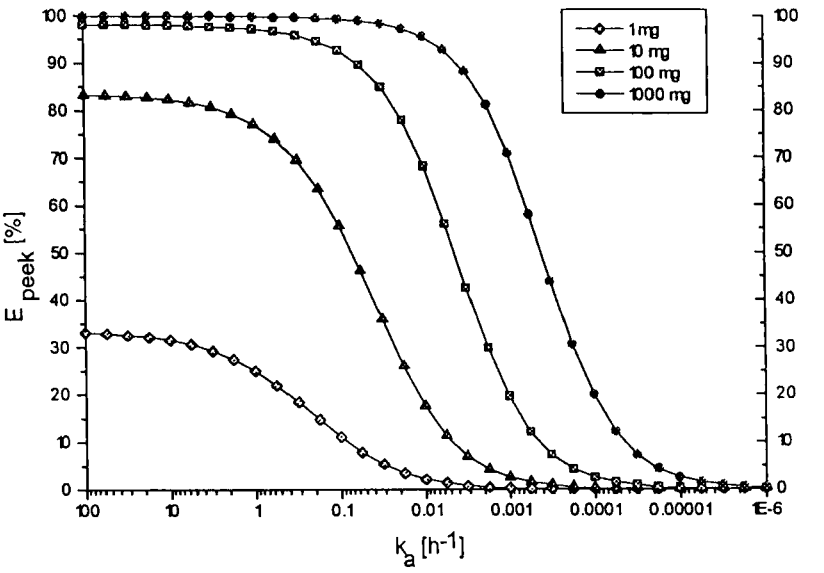

FIGURE 9

Relationship between first-order absorption rate constant k_a and maximum effect achieved (E_{peak}) for four different doses (1, 10 , 100 and 1000 mg.). Assumed pharmacokinetic parameters are k_e = 0.2 h^{-1} and Vd = 100 l, assumed pharmacodynamic parameters are E_{max} = 100 % and E_{50} = 0.01 mg/l.

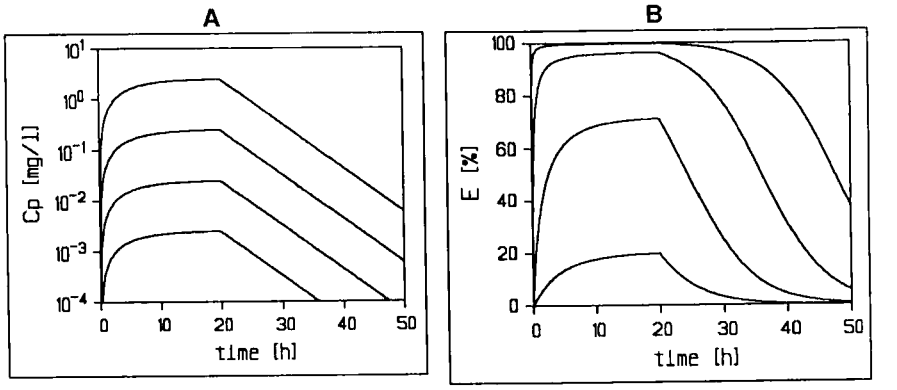

FIGURE 10

Pharmacokinetic (A) and pharmacodynamic (B) profiles for a drug administered in four different doses (1, 10, 100 and 1000 mg) by zero-order absorption over 20 hours. Assumed pharmacokinetic parameters are k_e = 0.2 h^{-1} and Vd = 100 l, assumed pharmacodynamic parameters are E_{max} = 100 % and E_{50} = 0.01 mg/l.

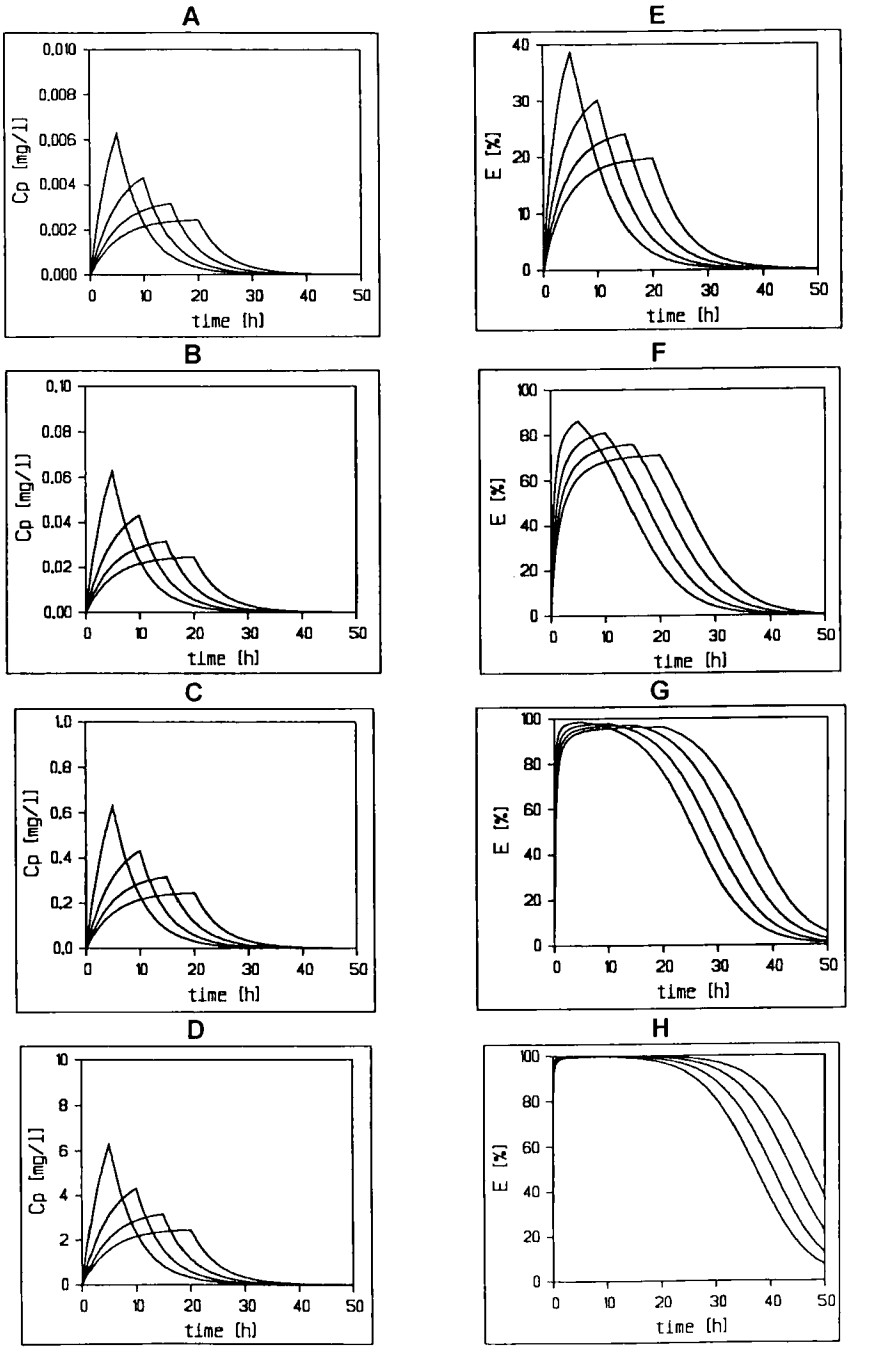

FIGURE 11

Pharmacokinetic (A-D) and pharmacodynamic (E-H) profiles for a drug administered by zero-order absorption in four different absorption rates (over 5, 10, 15 and 20 hours). Dose varied from 1 (A, E), 10 (B, F), 100 (C, G) and 1000 mg (D, H). Assumed pharmacokinetic parameters are k_e = 0.2 h^{-1} and Vd = 100 l, assumed pharmacodynamic parameters are E_{max} = 100 % and E_{50} = 0.01 mg/l.

important, they illustrate the fundamental differences between the conventional pharmacokinetic evaluation and the more therapeutically significant pharmacodynamic evaluation. More experimental data is needed to confirm these PK-PD models in well designed studies. However, it is exciting to notice the increase of papers and number of contributions in this field. Just as pharmacokinetics has become a routine discipline for drug evaluation, it seems certain that quantitative pharmacodynamics and PK-PD modeling will be a routine tool in the future to optimize drug use by designing rational dosage forms and dosage regimes.

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